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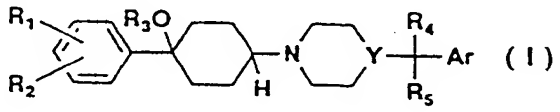
(54) **Piperazinyl-and piperidinyl-cyclohexanols.**

(57) Novel piperazinyl- and piperidinyl-cyclohexanols of formula I are useful as anxiolytic agents and have other psychotropic properties.



(I)

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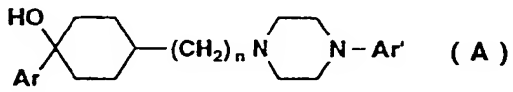
BACKGROUND

This invention generally pertains to piperazinyl- and piperidinylcyclohexanol compounds having anxiolytic and other psychotropic, bio-affecting properties and to their preparation and use. In some preferred embodiments, the invention is concerned with 1,4-disubstituted piperazine or piperidine derivatives wherein the 4-substituent is benzyl or substituted benzyl, and the 1-substituent is a 4-(1-aryl-cyclohexan-1-ol) moiety. These compounds and others structurally related thereto possess a unique serotonergic profile that makes them useful in the treatment of anxiety. Caprathe et al disclosed a series of piperazinyl-cyclohexanolcompounds characterized by structural formula A in U.S. Pat. No. 4,957,921. Formula A is:

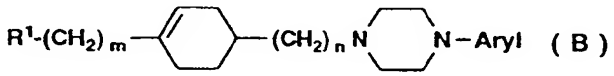


(A)

wherein n is 0 to 4 and Ar and Ar' are aryl or heterocyclic rings.

As can be seen, these earlier compounds are chemically distinguishable from the instant compounds on the basis of their chemical structures because they are aryl- or heteroaryl-piperazines, whereas the instant compounds are benzyl-or heteroarylmethyl-piperazines (when, in Formula I below, Y = N) or piperidines (when, in Formula I below, Y = CH). Additionally, these earlier compounds are biologically distinguishable from the instant compounds, since they possess dopaminergic properties, which are associated with undesirable side effects including Parkinsonism and extrapyramidal side effects such as catalepsy. Contrastingly, the instant compounds are serotonergic agents devoid of dopaminergic properties and the movement disorders often associated therewith.

Caprathe et al disclosed a series of piperazinyl-cyclohexene compounds characterized by structural formula B in U.S. Patent No. 4,975,445. Formula B is:

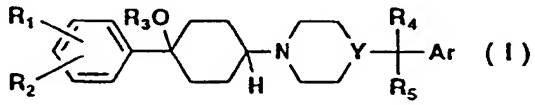


(B)

wherein R^1 is an aryl or heterocyclic ring, m is 0-2 and n is 0-4. Likewise, these compounds are structurally and biologically distinguishable from the instant compounds. Chemically, the reference compounds are aryl-piperazines, while the instant compounds are benzyl- or heteroarylmethyl-piperazines. Biologically, their dopaminergic properties distinguish them from applicants' compounds, which have serotonergic activity. Accordingly, the movement disorders associated with dopaminergic agents are avoided when the instant compounds are administered.

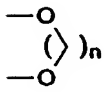
SUMMARY AND DETAILED DESCRIPTION OF THE INVENTION

In its broadest aspect, the invention is concerned with certain compounds which are substituted benzyl- or heteroarylmethyl-piperazinyl cyclohexanes or substituted benzyl or heteroarylmethyl piperidinyl cyclohexanes which are useful anxiolytic agents. The compounds conform to formula I:



(I)

wherein R_1 and R_2 are selected independently from H, halogen, CF_3 or C_{1-4} alkoxy groups except that R_1 and R_2 cannot both be H simultaneously; and R_1 and R_2, when on adjacent carbon atoms, can be taken together to form a



bridge (n = 1-3); R_3 is H or C_{1-4} alkyl; R_4 and R_5 are independently selected from H, C_{1-4} alkyl or phenyl; Y is N or CH; and Ar is a heteroaryl ring or a substituted or unsubstituted phenyl ring.

Compounds of formula I include all pharmaceutically acceptable salts and/or solvates thereof. The invention also encompasses all stereoisomers of compounds of formula I.

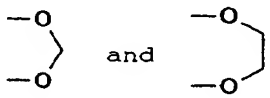
Pharmaceutically acceptable salts based on Formula I can be obtained using inorganic or organic acids such as sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, citric, acetic, benzoic, fumaric, cinnamic, mandelic, nitric, mucic, isethionic, palmitic, heptanoic and the like.

R_1 and R_2 may, either singly or in combination, be halogen atoms. Preferred halogens are Cl and F, with F being highly preferred.

While R_1 and R_2 may both be C_{1-4} alkoxy moieties, it is generally preferred that only one of them be alkoxy. Preferred alkoxy groups are those that contain not more than two carbon atoms. Thus, methoxy and ethoxy groups are preferred embodiments for R_1 and R_2.

Compounds in which one of R_1 and R_2 is F and the other is OCH_3 are very useful.

R_1 and R_2, when on adjacent carbon atoms, may be taken together to form a bridging group. It is preferred that the group be a 3- to 5-membered group containing 2 terminal oxygen atoms separated by a $-(CH_2)_n-$ (n = 1-3) linkage. Compounds having



bridges are highly preferred.

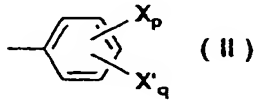
R_3 may be H or a C_{1-4} alkyl moiety. It is preferred that R_3 be H or contain no more than two carbon atoms. Accordingly, it is preferred that R_3 be H, CH_3 or C_2H_5, with H and CH_3 being highly preferred.

R_4 and R_5 are, as indicated above, selected independently from H, C_{1-4} alkyl and phenyl moieties. It is preferred that at least one of R_4 and R_5 be H, with the other being H or C_{1-2} alkyl (i.e., H, CH_3 or C_2H_5). It is highly preferred that both R_4 and R_5 be H, so that a methylene bridge is formed between the piperazine (Y = N) or piperidine (Y = CH) ring and the Ar group.

Y may be N or CH. While it may be either, the use of piperidines (wherein Y = CH) is preferred.

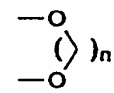
Ar may be any of a variety of compounds based upon a phenyl or heteroaryl ring. Useful heteroaryl groups include 2-thienyl, 2-furanyl and 1-methyl-2-pyrrolyl moiety.

Ar may also be an unsubstituted phenyl group or a substituted phenyl group of formula II:



(II)

wherein X and X' may be halogen (preferably Cl or F), nitro, amino, carboxamide, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} alkylthio or similar moieties, or X and X' can be taken together to form a



bridge (n = 1-3). The values p and q may be 0 to 5, with $p + q \leq 5$.

Ar may also be a heteroaryl group. Suitable heteroaryl groups contain O, S and/or N atoms and include 3- and 4-pyridinyl, 2-thienyl, 2-furanyl, and 1-methyl-2-pyrrolyl and similar moieties.

There are several groups of preferred compounds that fall within formula I.

One group is those compounds in which R_1 = F, R_2 and R_3 = H, and X = H, F, Cl, Br, or OCH_3

A second group is that in which R_1 = F, R_2 and R_3 = H and X and X' = F.

Another group is made up of those compounds in which R_1 and R_2 form an - OCH_2O- bridge and at least one of X and X' is F or OCH_3.

Yet another group consists of molecules in which R_1 and R_2 form a -OCH_2O-bridge, R_3 = C_1, and X and X' are both F.

Two highly preferred groups of compounds are those in which either:

(a) R_1 and R_2 form a -OCH_2O- bridge and X is F or OCH_3; or

(b) R_1 or R_2 is F or CF_3 and at least one of X and X' is F.

Preferred compounds of Formula I include:

Z-1-(1,3-benzodioxol-5-yl)-4-[4-(phenylmethyl)-1-piperidinyl]cyclohexanol;
Z-1-(4-methoxyphenyl)-4-[4-(phenylmethyl)-1-piperidinyl]cyclohexanol;
Z-1-(1,3-benzodioxol-5-yl)-4[4-(phenylmethyl)-1-piperazinyl)cyclohexanol;
Z-1-(4-methoxyphenyl)-4-[4-(phenylmethyl)-1-piperazinyl]cyclohexanol;
Z-1-[4-(1,3-benzodioxol-5-yl)-4-methoxycyclohexyl]-4-(phenyl-methyl)piperazine;
Z-1-(1,4-benzodioxan-6-yl)-4-[4-(phenylmethyl)-1-piperazinyl]cyclohexanol;
E-1-(1,4-Benzodioxan-6-yl)-4-[4-(phenylmethyl)-1-piperazinyl]cyclohexanol;
Z-1-(1,3-benzodioxol-5-yl)-4-[4-[(3-methoxyphenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-benzodioxol-5-yl)-4-[4-[(3-fluorophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-benzodioxol-5-yl)-4-[4-[(2-fluorophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-benzodioxol-5-yl)-4-[4-[(2-methylphenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-benzodioxol-5-yl)-4-[4-[(2-nitrophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-benzodioxol-5-yl)-4-[4-[(2-chlorophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-benzodioxol-5-yl)-4-[4-(2-thienylmethyl)-1-piperazinyl]cyclohexanol;
Z-1-(1,3-Benzodioxol-5-yl)-4-[4-((2,5-dichlorophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2,5-difluorophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2,3-difluorophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(3,5-difluorophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2-iodophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(1,3-benzodioxo-4-yl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(4-Fluorophenyl)-4-[4-[(3-methoxyphenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(4-Fluorophenyl)-4-[4-[(2-chlorophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-I-(4-Fluorophenyl)-4-[4-[(2,5-difluorophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-[(4-Trifluoromethyl)phenyl]-4-[4-[(2-chlorophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-[(4-Trifluoromethyl)phenyl]-4-[4-[(3-methoxyphenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2-fluoro-5-methoxyphenyl) methyl]-1-piperazinyl]cyclohexanol;
Z-1-(4-Fluorophenyl)-4-[4-[(2-fluoro-5-methoxyphenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,4-Benzodioxan-6-yl)-4-[4-[(3-methoxyphenyl)methyl]-1-piperidinyl]cyclohexanol;
Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(3-methoxyphenyl)methyl]-1-piperidinyl]cyclohexanol;
Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2,5-difluorophenyl)methyl]-1-piperidinyl]cyclohexanol;
Z-1-]4-(1,3-Benzodioxol-5-yl)-4-methoxy-1-cyclohexyl]-4-[(3-methoxyphenyl)methyl]piperidine;
Z-1-]4-(1,4-Benzodioxan-6-yl)-4-methoxy-1-cyclohexyl]-4-[3-(methoxyphenyl)methyl]piperidine fumarate;
Z-1-]4-(1,3-Benzodioxol-5-yl)-4-methoxy-1-cyclohexyl]-4-[(2,5-difluorophenyl)methyl]piperidine fumarate;
Z-1-(4-Fluorophenyl)-4-[4-(phenylmethyl)-1-piperidinyl] cyclohexanol;
Z-1-(4-Fluorophenyl)-4-[4-[(3-methoxyphenyl)methyl]-1-piperidinyl] cyclohexanol;
Z-1-(4-Fluorophenyl)-4-[4-[(2,5-difluorophenyl)methyl]-1-piperidinyl]cyclohexanol;
Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2-bromophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-Benzodioxol-5-yl)-4-[4-(diphenylmethyl)-1-piperazinyl] cyclohexanol;
Z-1-(1,3-Benzodioxol-5-yl)-4-[4-(1-phenylethyl)-1-piperazinyl] cyclohexanol;
Z-1-[4-(4-Fluorophenyl)-4-methoxy-1-cyclohexyl]-4-[(3-methoxyphenyl)methyl]piperazine;
Z-1-[4-(4-Fluorophenyl)-4-methoxy-1-cyclohexyl]-4-[(3-methoxyphenyl)methyl]piperazine; and the like.

Another aspect of the present invention provides a method for treating a mammal afflicted with anxiety or panic disorders which comprises administering systematically to said mammal a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable acid addition salt thereof.

Although the dosage and dosage regimen must in each case be carefully adjusted, utilizing sound professional judgement and considering the age, weight and condition of the recipient, the route of administration and the nature and gravity of the illness, generally the daily dose will be from about 0.01 to about 10 mg/kg, preferable 0.1 to 2 mg/kg, when administered parenterally and from about 1 to 50 mg/kg, when administered orally. In some instances a sufficient therapeutic effect can be obtained at lower doses

while in others, greater doses will be required. Systemic administration refers to oral, rectal, transnasal, transdermal, and parenteral (i.e. intramuscular, intravenous, and subcutaneous). Generally it will be found that when a compound is administered orally, a greater quantity of the active agent is required to produce the same effect as a similar quantity given parenterally. In accordance with good clinical practice, it is preferred to administer the present compounds at a concentration level that will produce effective anxiolytic effects without causing any harmful or untoward side effects.

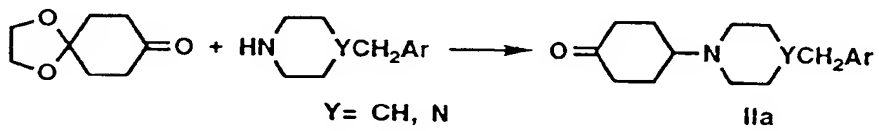
The compounds of the present invention may be administered for anxiolytic purposes either as individual therapeutic agents or as mixtures with other therapeutic agents. Therapeutically, they are generally given as pharmaceutical compositions comprised of an anxiolytic amount of a compound of Formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. Pharmaceutical compositions which provide from about 1 to 500 mg of the active ingredient per unit dose are preferred and are conventionally prepared as tablets, lozenges, capsules, powders, aqueous or oily suspensions, syrups, elixirs, and aqueous solutions.

The compounds of the invention are also useful, in the dosages referred to above, in the prophylactic treatment of migraine (i.e., for the prevention of migraine headaches. The nature of the pharmaceutical composition employed will, of course, depend on the desired route of administration. For example, oral compositions may be in the form of tablets or capsules and may contain conventional excipients such as binding agents (e.g. starch) and wetting agents (e.g. sodium lauryl sulfate). Solutions or suspensions of a Formula I compound with conventional pharmaceutical vehicles are employed for parenteral compositions such as aqueous solution for intravenous injection or an oily suspension for intramuscular injection.

Compounds of Formula I can be prepared via processes set out below:

SCHEME a:

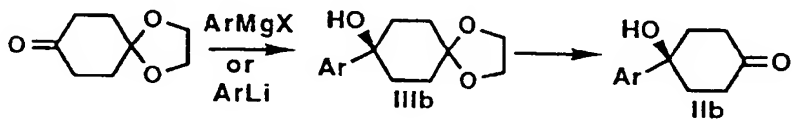
(Examples 1 & 2)



Scheme a shows the preparation of intermediate compounds IIa by condensation of cyclohexan-1,4-dione mono-ethylene ketal with a 4-arylmethylpiperidine or a 1-arylmethylpiperazine under reductive alkylation condition such as, titanium isopropoxide/$NaBH_4$, sodium cyanoborohydride, sodium triacetoxyborohydride and the like. The resulting ketals are cleaved under acidic conditions such as, acetone/HCl, THF/HCl, acetone/H_2SO_4, THF/H_2SO_4, dioxane/HCl and the like. Other methods known to those skilled in the art may be also used.

SCHEME b:

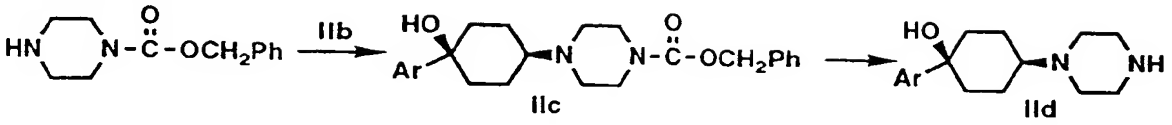
(Examples 3, 4, & 7-10)



The intermediate compounds IIb are prepared as shown in Scheme b. Reaction of cyclohexan-1,4-dione mono-ethyleneketal with organometallic reagents, such as Grignard reagents, aryl lithium reagents and the like, furnish the 4-aryl-4-hydroxy-cyclohexanone ketals IIIb. These reactions are generally carried out in solvents such as tetrahydrofuran, diethyl ether, dimethoxyethane, dioxane, ethylene glycol dimethylether and the like at temperatures from -80 to 30 °C. The ketals are cleaved by acid catalysis to give the 4-aryl-4-hydroxycyclohexanones IIb. Acids suitable for this hydrolysis include but are not limited to hydrochloric, sulfuric, acetic, phosphoric, para-toluenesulfonic, methanesulfonic, benzoic and the like.

SCHEME c:

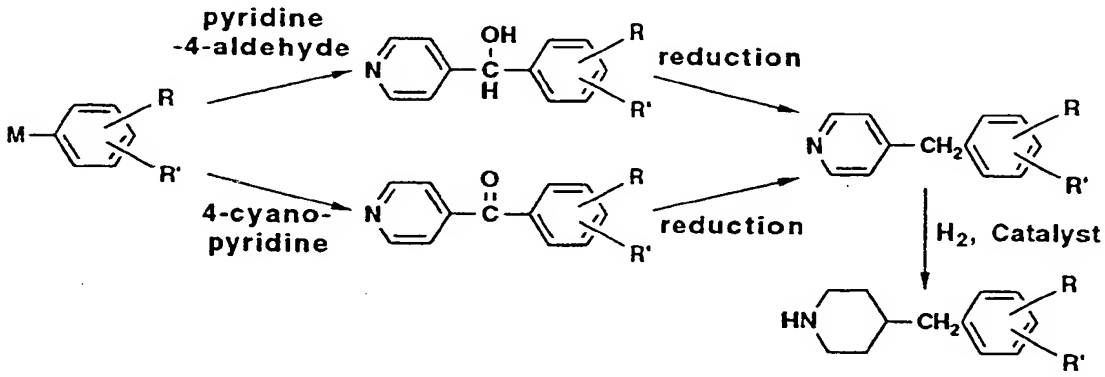
(Examples 5 & 6)



The preparation of the Z-1-aryl-4-piperazinylcyclohexanols is shown in Scheme c. The 4-aryl-4-hydroxycyclohexanones IIb, prepared as described in Scheme b, are reductively coupled with a mono-protected piperazine, such as carbobenzyloxypiperazine, under the usual conditions as described in Scheme a above to provide the protected Z-1-aryl-4-piperazinyl-cyclohexanols. Other suitable protecting groups for piperazine include, but are not limited to, methylcarbamate, ethylcarbamate, t-butylcarbamate, acetyl, formyl, propionyl, methanesulfonyl, p-toluenesulfonyl, benzyl, appropriately substituted benzyl and the like. The 1-aryl-4-piperazinylcylohexanols are generally obtained as a mixture of diastereomers which may be readily separated by methods known to those skilled in the art. These methods include but are not limited to recrystallization, chromatographic separation using common absorbants such as silica (silica gel), alumina and the like. The protected Z-1-aryl-4-piperazinylcyclohexanols are deprotected by the usual methods known to those skilled in the art. These methods include but are not limited to catalytic reduction, dissolving metal reduction, chemical reduction, basic hydrolysis, acid hydrolysis, acid cleavage, chemical removal and the like.

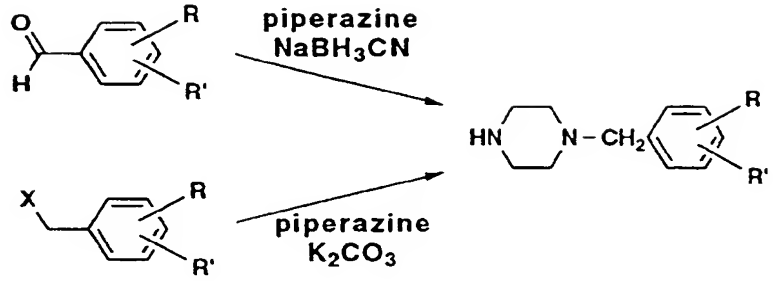
Scheme d:

(Examples 11-13)



Scheme d shows the preparation of the substituted arylmethyl-piperazines. Reaction of either pyridine-4-aldehyde or 4-cyanopyridine with appropriate organometallic reagents, such as Grignard reagents, aryl lithium reagents and the like, furnish the alcohol and ketone intermediates shown in Scheme d. These organometallic reactions are generally carried out as described under Scheme b. The alcohol or ketone intermediates are reduced to the substituted arylmethyl-pyridine under conditions generally known to those skilled in the art. Such catalytic reduction conditions include catalysts such as palladium on carbon, and the like, and sources of hydrogen such as hydrogen gas, ammonium formate, or hydrazine, and the like. Further reduction of the pyridine, generally under acidic conditions using a catalyst such as platinum oxide, and the like, provide the desired substituted-arylmethylpiperazines.

Scheme e:
(Example 14)

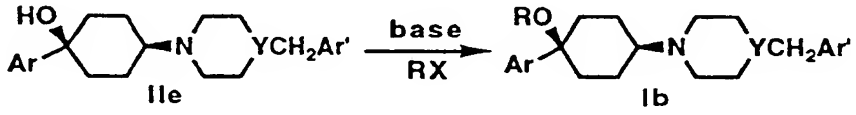


Scheme e shows the preparation of the substituted-arylmethylpiperazines. The appropriately-substituted aryl aldehyde is reductively coupled with piperazine, or a mono-protected piperazine, such as carbobenzyloxypiperazine, under the usual conditions as described in Scheme c above to provide the substituted-arylmethylpiperazines. Other suitable protecting groups for piperazine are described under Scheme c. The protected arylmethylpiperazines are deprotected by the usual methods described under Scheme c. Alternatively, an appropriately-substituted arylmethyl halide can be used to alkylate piperazine under standard conditions as are described more fully under Scheme h.

SCHEME f:
(Examples 15-18 & 20)

Scheme f shows the preparation of the desired 1-aryl-4-(4-arylmethyl-1-piperidinyl)cyclohexanols and 1-aryl-4-(4-arylmethyl-1-piperazinyl)cyclohexanols 1a by addition of organometallic reagents, such as aryl Grignard reagents or aryl lithium reagents and the like to the 4-(4-arylmethyl-1-piperidinyl)cyclohexanones and the 4-(4-arylmethyl-1-piperazinyl)cyclohexanones. The reaction may be carried out in an inert solvent such as tetrahydrofuran, diethyl ether, dimethoxyethane, diethyleneglycol dimethyl ether and the like, at temperatures from -100 to 25 °C. The desired compounds are generally obtained as diastereomeric mixtures that may be separated as described for Scheme c above.

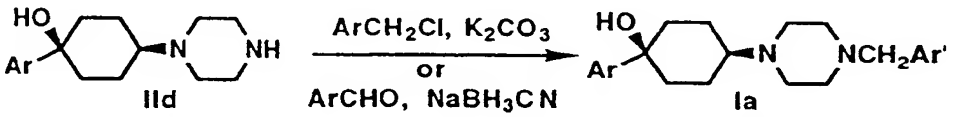
SCHEME g:
(Example 19)



The preparation of the 1-(4-aryl-4-alkoxy-1-cyclohexyl)-4-(arylmethyl)piperidines and the 1-(4-aryl-4-alkoxy-1-cyclohexyl)-4-(arylmethyl)piperazines is described in Scheme g. The 1-aryl-4-(4-arylmethyl-1-piperidinyl)cyclohexanols and the 1-aryl-4(4-arylmethyl-1-piperazinyl)cyclohexanols Ia are reacted with an alkylating agent and an appropriate base in a suitable solvent such as tetrahydrofuran, diethyl ether,

dimethylformamide, dimethylacetamide, dimethyl sulfoxide, dioxane, dimethoxyethane, ethylene glycol dimethyl ether and the like to give the desired products Ib. Appropriate bases for this reaction include but are not limited to sodium hydride, potassium hydride, calcium hydride, lithium hydride, sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, calcium hydroxide, butyl lithium, methyl lithium, phenyl lithium and the like. Alkylating agents include but are not limited to methyl iodide, ethyl iodide, dimethyl sulfate, diethyl sulfate, propyl iodide, propyl bromide, methyl trifluoromethanesulfonate, ethyl trifluoromethanesulfonate, methyl trifluoroacetate, ethyl trifluoroacetate, and the like. Other methods known to those skilled in the art may also be used.

SCHEME h:
(Examples 21-27)



Scheme h shows the preparation of 1-aryl-4-(4-arylmethyl-1-piperazinyl)cyclohexanols Ia (Y = N) from the 1-aryl-4-piperazinylcyclohexanols IId. The 1-aryl-4-piperazinecyclo-hexanols may be alkylated under standard conditions known to those skilled in the art, such as using arylmethyl halides, arylmethyl para-toluenesulfonates, arylmethyl methanesulfonates and the like, in the presence of a base, such as potassium carbonate in an inert solvent such as acetonitrile, tetrahydrofuran, dimethoxyethane, dioxane, acetone, dichioroethane, dimethylformamide, dimethylacetamide, dimethyl sulfoxide and the like. Likewise, sodium carbonate, potassium bicarbonate, sodium bicarbonate, triethylamine, tripropylamine tributylamine, pyridine and the like may be also used as bases. Additionally, the 1-aryl-4-piperazinylcyclohexanols IIa may be reductively alkylated with aryl aldehydes using sodium cyanoborohydride, sodium triacetoxyborohydride, lithium borohydride, sodium borohydride, sodium borohydride/titanium isopropoxide and similar reducing agents to provide the 1-aryl-4-(4-arylmethyl-1-piperazinyl)cyclohexanols Ia. Aryl ketones may be used in place of the aryl aldehydes to provide 1-aryl-4-[4-(1-aryl-1-alkyl)piperazinyl]cyclohexanols.

Alternatively, the 1-aryl-4-(4-arylmethyl-1-pipera-zinyl)cyclohexanols Ia may be obtained from the 1-aryl-4- piperazinyl)cyclohexanols IIb by preparation of an aryl carboxamide followed by reduction to the products Ia. Appropriate conditions for preparation of the amides include reaction of an aroyl halide with the 1-aryl-4-piperazinylcyclohexanols in the presence of a suitable base, such as triethylamine, tripropylamine, tributylamine, pyridine, potassium carbonate, sodium carbonate, potassium bicarbonate, sodium bicarbonate and the like. Suitable solvents for this reaction include tetrahydrofuran, dimethoxyethane, benzene, toluene, xylene, acetonitrile, acetone, dioxane, dimethylformamide, dimethyl-acetamide, dimethyl sulfoxide and the like. The reaction is typically carried out at temperatures from 30 to 120 °C. The aryl carboxamides may also be prepared by reaction of an aryl carboxylic acid with a coupling reagent such as carbonyl diimidazole followed by reaction with the 1-aryl-4-piperazinyl-cyclohexanols IId. Additionally the arylcarboxamides may be obtained by reaction of the 1-aryl-4-piperazinylcyclohexanols with an aryl carboxylic acid ester in an suitable solvent, such as acetonitrile, acetone, dioxane, tetrahydrofuran, dimethoxyethane, benzene, toluene, xylene, dichloroethane, dimethylformamide, dimethylacetamide, dimethyl sulfoxide and the like at temperatures from 25 to 150 °C. The intermediate arylcarboxamides may be reduced with reagents such as, lithium aluminum hydride, diisobutyl aluminum hydride, diborane, sodium bis(2-methoxyethoxy)aluminum hydride and the like in an appropriate solvent such as tetrahydrofuran, dimethoxyethane, diethyl ether, dioxane, benzene, toluene, xylene, diethylene glycol dimethyl ether and the like. The reduction may be carried out at temperatures from 0 to 120 °C. Other methods known to those skilled in the art for the preparation and reduction of amides may also be used.

EXAMPLES

The compounds which constitute this invention, their methods of preparation and their biological actions will be better appreciated after consideration of the following examples, which are given for the purpose of illustration only and are not be construed as limiting the invention. In the following examples, temperatures are expressed in degrees Celsius and melting points are uncorrected. Unless stated otherwise, all percentages given herein are weight percentages based on total composition weight.

The following examples describe in detail the preparation of compounds of Formula I, as well as Formula II synthetic intermediates in each process. It will be apparent to those skilled in the art that modifications, both of materials and methods, will allow preparation of other compounds disclosed herein.

A. Preparation of Formula II intermediate compounds

Some representative procedures for preparation of synthetic intermediate compounds utilized above are given herein below. Most starting materials and certain intermediates are either commercially available or procedures for their synthesis are readily available in the chemical literature, allowing their full utilization by one skilled in the art of organic synthetic chemistry.

EXAMPLE 1

4-[4-(Phenylmethyl)-1-piperidinyl]cyclohexanone (IIa; Y = CH)

Titanium(IV) isopropoxide (16.5 ml) was added to a mixture of 4-benzylpiperidine (8.76 g, 50 mmole) and 1,4-cyclohexanedione monoethylene ketal (7.81 g, 50 mmole) and gently heated. After stirring for 18 hr, the yellow oil was diluted with ethanol (100 ml) and $NaBH_4$ (2 g) was added. The mixture was stirred for 4 hr and water (10 ml) was added to precipitate the TiO_2. The mixture was filtered and filtrate was concentrated *in vacuo* to give 15.87 g (100%) of the crude ketal intermediate as a tan solid. This intermediate was stirred in a mixture of THF (75 ml) and 50% H_2SO_4 (75 ml) for 20 hr. The acid was neutralized with NaOH (50%) and Na_2CO_3 with ice bath cooling. The ketone product was extracted with ether and concentrated *in vacuo*. This yellow oil was Kugelrohr distilled to give a colorless oil that solidified upon standing to give 8.30 g (61.3%) of the ketone as colorless crystals.

EXAMPLE 2

4-[4-(Phenylmethyl)-1-piperazinyl]cyclohexanone (IIa; Y = N)

Titanium(IV) isopropoxide (74 ml) was added to a mixture of 1-benzylpiperazine (35.2 g, 200 mmole) and 1,4-cyclohexanedione monoethylene ketal (31.2 g, 200 mmole) and stirred until no ketone absorption was observed in the IR spectrum. The yellow oil was diluted with ethanol (200 ml) and $NaBH_4$ (7.6 g, 200 mmole) was added. The mixture was stirred for 16 hr and water (37 ml) was added to precipitate the TiO_2. The mixture was filtered and filtrate was concentrated *in vacuo*. The residue was dissolved in ether and the solution was washed with 1N HCl. The acid washes were basified with K_2CO_3, and the basic mixture extracted with methylene chloride. The extracts were dried over K_2CO_3 and concentrated *in vacuo* to give 56.5 g of ketal product, which was stirred in a mixture of THF (300 ml) and 50% H_2SO_4 (300 ml) for 2 hr. The solution was diluted with water (500 ml) and carefully basified with K_2CO_3. The basic mixture was extracted with ether and the extracts dried over sodium sulfate. Concentration *in vacuo* of the extract, followed by recrystallization from isopropyl ether, gave the product (41 g, 71 %, mp: 83-85 °C)

EXAMPLE 3

8-(1,3-Benzodioxol-5-yl)-1,4-dioxaspiro[4.5]decan-8-ol (IIIb)

A solution of 1,4-cyclohexanedione monoethylene ketal (31.2 g, 0.2 mole) in 100 ml dry THF was added to a -60 °C solution of the Grignard reagent prepared from magnesium metal (7.2 g, 0.3 mole) and 5-bromo-1,3-benzodioxole (60.3 g, 0.3 mole). The mixture was allowed to warm to 25 °C and quenched with saturated NH_4Cl and extracted with ether. The extracts were dried with Na_2SO_4 and the solvent removed *in vacuo*. The residue was crystallized from isopropyl ether to give the product (47.5 g, 85%, m.p: 103-104 °C).

EXAMPLE 4

4-(1,3-benzodioxol-5-yl)-4-hydroxycyclohexanone (IIb)

A solution of 8-(1,3-benzodioxol-5-yl)-1,4- dioxaspiro[4.5]decan-8-ol (IIIb; 5 g, 18 mmole) in 75 ml acetone, 1 ml 12 N HCl, and 50 ml water, was stirred for 2 hr. After dilution with an additional 50 ml water

the solid was collected to give the product (4.0 g, 95%, mp: 166-168 °C).

EXAMPLE 5

Phenylmethyl Z-4-[4-(1,3-benzodioxol-5-yl)-4-hydroxy-cyclohexyl]-1-piperazinecarboxylate (IIc)

A mixture of phenylmethyl 1-piperazinecarboxylate (5.65 g, 25.7 mmole), titanium(IV) isopropoxide (17 ml, 50 mmole), and 4-(1,3-benzodioxol-5-yl)-4-hydroxycyclohexanone (6.0 g, 25.7 mmole) was stirred for 18 hr. The mixture was dissolved in 50 ml ethanol and sodium borohydride (1.0 g, 25.7 mmole) was added. After stirring for 16 hr the mixture was quenched with 15% sodium hydroxide solution (6 ml). The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was acidified with 1N HCl to give a solid. The solid was collected and suspended in water. The mixture was basified with sodium hydroxide and extracted with methylene chloride. The extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The residue was crystallized from isopropyl ether to give the product (2.4 g, 22%, mp: 122-124 °C).
Calc'd for $C_{25}H_{30}N_2O_5 \cdot 0.5H_2O$: C, 67.10%; H, 6.99%; N, 6.26%. Found: C, 67.18%; H, 6.8%; N, 6.26%.

EXAMPLE 6

Z-1-(1,3-Benzodioxol-5-yl)-4-(1-piperazinyl)cyclohexanol (IId)

A mixture of phenylmethyl Z-4-[4-(1,3-benzodioxol-5-yl)-4-hydroxycyclohexyl]-1-piperazine-carboxylate (0.44 g, 1 mmole) and 10% palladium on charcoal (0.1 g) was hydrogenated for 1 hr. The catalyst was filtered off and the filtrate concentrated *in vacuo*. The residue was crystallized from isopropyl acetate to give the product (0.30 g, 93.5%, mp: 198-199 °C).
Calc'd for $C_{17}H_{24}N_2O_3$: C, 65.16%; H, 8.05%; N, 8.94%.
Found: C, 65.27%; H, 7.69%; N, 8.83%.

EXAMPLE 7

8-(4-Fluorophenyl)-1,4-dioxaspiro[4.5]decan-8-ol

This compound was prepared from 1,4-cyclohexanedione monoethylene ketal (6.24 g, 40 mmole) and 4-fluorophenyl magnesium bromide (60 mmole) in a manner similar to example 3. The crude product was crystallized from hexane to give the product (8.9 g, 88%).

EXAMPLE 8

8-[4(-Trifluoromethyl)phenyl]-1,4-dioxaspiro[4.5]decan-8-ol

This compound was prepared from 1,4-cyclohexanedione monoethylene ketal (10.9 g, 70 mmole) and the Grignard reagent prepared from 4-bromobenzotrifluoride (25.0 g, 110 mmole) and magnesium (2.7 g, 110 mmole) in a manner similar to example 3. The crude product was crystallized from petroleum ether to give the product (20 g, 94.8%).
Calc'd. for $C_{15}H_{17}F_3O_3$: C, 59.60%; H, 5.67%.
Found: C, 59.77%; H, 5.62%.

EXAMPLE 9

4-(4-Fluorophenyl)-4-hydroxycyclohexanone

This compound was prepared from 8-(4-fluorophenyl)-1,4-dioxaspiro[4.5]decan-8-ol (2.5 g, 10 mmole) in a manner similar to example 4. The crude material was crystallized from isopropyl ether to give the product (2.0 g, 95%, mp: 118-119 °C).
Calc'd. for $C_{12}H_{13}FO_2$: C, 69.22%; H, 6.30%.
Found: C, 69.32%; H, 6.34%.

EXAMPLE 10

4-[4-(Trifluoromethyl)phenyl]-4-hydroxycyclohexanone

This compound was prepared from 8-[4(-trifluoromethyl)phenyl]-1,4-dioxaspiro[4.5]decan-8-ol (10 g, 33 mmole) in a manner similar to example 4. The crude material was crystallized from isopropyl ether to give the product (7.5 g, 90.4%).
Calc'd. for $C_{13}H_{13}F_3O_2$: C, 60.47%; H, 5.71%.
Found: C, 60.63%; H, 4.99%.

EXAMPLE 11

4-(3-Methoxybenzyl)piperidine

Step 1

A solution of 4-cyanopyridine in THF was added to the Grignard reagent prepared from 3-bromoanisole (37.4 g, 200 mmole) and magnesium (4.8 g, 200 mmole) in THF (400 ml) at -78 °C. The solution was allowed to warm to 25 °C and quenched with ammonium chloride solution. The organic layer was separated and washed with water and 3N hydrochloric acid. The acid washes were stirred for 0.5 hr and neutralized with 50% sodium hydroxide. The basic mixture was extracted with ether. The extracts were dried and concentrated *in vacuo*. The crude material was crystallized from hexane to give 4-(3-methoxybenzoyl)-pyridine (27 g, 63.3%).

Step 2

Ammonium formate (25 g) was added to a mixture of 4-(3-methoxybenzoyl)pyridine (27 g, 127 mmole) and 10% palladium on charcoal (7 g) in acetic acid (250 ml). The mixture was heated at reflux for 0.5 hr. The mixture was cooled and diluted with an equal volume of methylene chloride. The catalyst was removed and the solution concentrated *in vacuo*. The residue was dissolved in water and basified with sodium hydroxide. The mixture was extracted with ether. The extracts were dried and concentrated *in vacuo* to give the crude 4-(3-methoxybenzyl)pyridine (25 g, 98.8%) which was used without purification in the next step.

Step 3

A mixture of 4-(3-methoxybenzyl)pyridine (25 g, 126 mmole) and platinum oxide (2.4 g) in acetic acid (250 ml) was hydrogenated for 2 hr. The catalyst was removed and the solution concentrated *in vacuo*. The residue was dissolved in water and the solution basified with sodium hydroxide. The basic mixture was extracted with ether. The extracts were dried and concentrated *in vacuo*. The residue was vacuum distilled to give 4-(3-methoxy-benzyl)piperidine as an oil (22.6 g, 87.6%). A sample of the hydrochloride was prepared in ether (mp: 146-147 °C).
Calc'd. for $C_{13}H_{19}NO \cdot HCl$: C, 64.59%; H, 8.34%; N, 5.80%.
Found: C, 64.38%; H, 8.34%; N, 5.66%.

EXAMPLE 12

4-(2,5-Difluorobenzyl)piperidine

Step 1

Butyl lithium (70 ml of 2.22M solution, 155 mmole) was added to a solution of pentamethyl-diethylenetriamine (23.3 ml, 155 mmole) in THF (250 ml) at - 70 °C. The solution was stirred for 5 min and 1,4-difluorobenzene (17.7 g, 155 mmole) in THF was added at -70 °C. The solution was stirred for 2 hr during which time it was cooled to -75 °C and 4-cyanopyridine (15.6 g, 150 mmole) in THF was added at - 75 °C. The mixture was allowed to warm to 25 °C slowly and then quenched with ammonium chloride solution. The mixture was diluted with ether and the organic layer was separated. The organic layer was washed with water and 3N hydrochloric acid. The acid washes were stirred for 2 hr and basified with sodium hydroxide. The basic mixture was extracted with ether and the ether solution concentrated *in*

vacuo. The crude product was purified by chromatography on silica eluting with ethyl acetate-hexane (20:1) to give 4-(2,5-difluorobenzoyl)pyridine (16.9 g, 51.5%).

Step 2

A mixture of 4-(2,5-difluorobenzoyl)pyridine (7.3 g, 33.3 mmole) and 10% palladium on charcoal in trifluoroacetic acid (50 ml) was hydrogenated for 24 hr. The catalyst was removed and the solution concentrated *in vacuo*. The residue was dissolved in water and basified with sodium hydroxide. The basic mixture was extracted with ether and the ether extracts concentrated *in vacuo*. The crude 4-(2,5-difluorobenzyl)pyridine was used without purification in the next step.

Step 3

A mixture of platinum oxide (.5 g) and 4-(2,5-difluoro-benzyl)pyridine from above in acetic acid (100 ml) was hydrogenated for 3 hr. The catalyst was removed and the solution concentrated *in vacuo*. The residue was dissolved in water and the solution basified with sodium hydroxide. The basic mixture was extracted with ether and the extracts concentrated *in vacuo*. The crude oil was vacuum distilled to give the product (5.1 g, 72.9%, bp: 110 °C). A sample of the hydrochloride was prepared in ether(mp: 146-147 °C).
Calc'd. for $C_{12}H_{15}F_2N \cdot HCl$: C, 58.19%; H, 6.52%; N, 5.66%.
Found: C, 58.14%; H, 6.56%; N, 5.59%.

EXAMPLE 13

4-(2-Fluoro-5-methoxybenzyl)piperidine

Step 1.

Butyl lithium (47.5 ml of 2.22M solution, 105.6 mmole) was added slowly to a solution of pentamethyl-diethylenetriamine (15 ml) and 4-fluoroanisole (12.61 g, 0.1 mole) in THF (150 ml) at -70 °C. The solution was stirred for 2 hr at -75 °C and a solution of pyridine-4-aldehyde (9.55 ml, 0.1 mole) in THF was added at - 75 °C. The mixture was allowed to warm to 25 °C slowly and then quenched with ammonium chloride solution. The mixture was diluted with ethyl acetate and the organic layer was separated. The organic layer was washed with water and 3N hydrochloric acid. The acid washes were then basified with sodium hydroxide and extracted with ether and the ether solution concentrated *in vacuo*. The crude product was recrystallized from 80% ethanol to give (2-fluoro-5-methoxy-phenyl)-4-pyridylmethanol as a white powder (12.22 g + 3.12 g second crop, 65.8% total yield).

Step 2

A mixture of (2-fluoro-5-methoxyphenyl)-4-pyridylmethanol and 10% palladium on charcoal in trifluoroacetic acid was hydrogenated similar to example 12, step 2. The catalyst was removed and the solution concentrated *in vacuo*. The residue was dissolved in water and basified with sodium hydroxide. The basic mixture was extracted with ether and the ether extracts concentrated *in vacuo*. The crude 4-(2-fluoro-5-methoxybenzyl)pyridine was used without purification in the next step.

Step 3

A mixture of 4-(2-fluoro-5-methoxybenzyl)pyridine (7.7 g, 35.5 mmole) and platinum oxide (0.7 g) in acetic acid (75 ml) was hydrogenated for 3 hr. The catalyst was removed and the acetic acid removed *in vacuo*. The residue was dissolved in water and the solution basified with sodium hydroxide. The basic mixture was extracted with ether. The extracts were dried and concentrated *in vacuo*. The residue was vacuum distilled to give the product (6 g, 75.9%).

EXAMPLE 14

4-(2-Fluoro-5-methoxybenzyl)piperazine

A solution of 2-formyl-4-methoxyfluorobenzene (5.0 g, 33 mmole, J. Organic Chem. 53 (14), p 3145 (1988)), piperazine (25.88 g, .3 mole), and sodium cyanoborohydride (3.08 g, 50 mmole) in ethanol (400 ml) was refluxed for 18 hr. The ethanol was removed in vacuo and the residue dissolved in water. The crude product was extracted from the aqueous mixture using methylene chloride. The methylene chloride extracts were concentrated in vacuo and the residue dissolved in 1 N HCl. The acidic solution was extracted with methylene chloride and then made basic with sodium hydroxide. The product was extracted from the basic aqueous solution with methylene chloride. Concentrating the methylene chloride extracts in vacuo gave the product as a light yellow oil (3.63 g, 50%).

B. Preparation of Compounds of Formula I

EXAMPLE 15

Z-1-(1,3-Benzodioxol-5-yl)-4-[4-(phenylmethyl)-1-piperidinyl] cyclohexanol

A solution of 4-[4-(phenylmethyl)-1-piperidinyl]cyclohexanone (2.5 g, 9.23 mmole) in dry THF (20 ml) was added to the Grignard reagent prepared from magnesium metal (0.50 g. 20.5 mmole) and 5-bromo-1,3-benzodioxole (2.84 g, 14.1 mmole) in dry THF (25 ml). The reaction mixture was stirred for 1 hr before being quenched with saturated NH_4Cl and extracted with ether. The ether extracts were dried with brine and concentrated *in vacuo*. The crude product was recrystallized twice from 20% ethyl acetate/c-hexane and dried *in vacuo* to give fluffy white crystals (1.25 g, 34.5 %, mp: 187-190.5 °C).
Calc'd for $C_{25}H_{31}NO_3$: C, 76.30%; H, 7.94%; N, 3.56%.
Found: C, 76.30%; H, 8.11%; N, 3.76%.

EXAMPLE 16

Z-1-(4-Methoxyphenyl)-4-[4-(phenylmethyl)-1-piperidinyl]cyclohexanol.

This compound was prepared in a Grignard reaction of 4-methoxyphenyl magnesium bromide (10 mmole) with 4-[4-(phenyl-methyl)-1-piperidinyl]cyclohexanone (5.9 mmole) in a manner similar to the above procedure. The crude product was recrystallized twice from 10% ethyl acetate/c-hexane to give white crystalline flakes (0.50 g, 22 %, mp: 177-179 °C).
Calc'd. for $C_{25}H_{33}NO_2$: C, 79.11%; H, 8.77%; N, 3.69%.
Found: C, 79.41%; H, 8.82%; N, 3.64%.

EXAMPLE 17

Z-1-(1,3-Benzodioxol-5-yl)-4-[4-(phenylmethyl)-1-piperazinyl]- cyclohexanol

This compound was prepared in a Grignard reaction of 1,3-benzodioxol-5-yl magnesium bromide with 4-[4-(phenylmethyl)-1-piperazinyl]cyclohexanone in a manner similar to the above procedure. The crude material was recrystallized from isopropyl acetate to give the product in a 22% yield (mp: 167-168 °C).
Calc'd. for $C_{24}H_{30}N_2O_3$: C, 73.07%; H, 7.67%; N, 7.11%.
Found: C, 73.05%; H, 7.67%; N, 7.09%.

EXAMPLE 18

Z-1-(4-Methoxyphenyl)-4-[4-(phenylmethyl)-1-piperazinyl]cyclohexanol

This compound was prepared in a Grignard reaction of 4-methoxyphenyl magnesium bromide with 4-[4-(phenylmethyl)-1-piperazinyl]cyclohexanone in a manner similar to the above procedure. The crude material was recrystallized from isopropyl acetate to give the product in a 50 % yield (mp: 179-180 °C).
Calc'd. for $C_{24}N_{32}N_2O_2$: C, 75.76%; H, 8.48%; N, 7.37%
Found: C, 75.79%; H, 8.65%; N, 7.35%

EXAMPLE 19

Z-1-[4-(1,3-Benzodioxol-5-yl)-4-methoxycyclohexyl]-4-(phenyl-methyl)piperazine

Sodium hydride (0.1 g, 2.5 mmole) was added to a solution of Z-1-(1,3-benzodioxol-5-yl)-4-[4-(phenylmethyl)-1-piperazinyl]cyclohexanol (1.0 g, 2.5 mmole) in dry THF (10 ml). Alter stirring for 1 hr the mixture was cooled to 5 °C and iodomethane (0.36 g, 2.5 mmole) added and the mixture allowed to stir for 18 hr. The mixture was diluted with water (25 ml) and extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The insoluble quaternary biproducts were removed by trituration with isopropanol. The isopropanol was then removed *in vacuo*. Starting material was removed by trituration with ether and the ether filtrate was chromatographed on silica using methanol/CH_2Cl_2 (1:50) to give a solid (50 mg, 5%, mp: 108-109 °C)
Calc'd. for $C_{25}H_{32}N_2O_3 \cdot 0.5H_2O$: C, 71.91%; H, 7.97%; N, 6.71.
Found: C, 71.71%; H, 7.50%; N, 6.62.

EXAMPLE 20

Z-1-(1,4-Benzodioxan-6-yl)-4-[4-(phenylmethyl)-1-piperazinyl]cyclohexanol, and E-1-(1,4-Benzodioxan-6-yl)-4-[4-(phenylmethyl)-1-piperazinyl]cyclohexanol.

These compounds were prepared in a Grignard reaction of 1,4-benzodioxan-6-yl magnesium bromide and 4-[4-(phenylmethyl)1-piperazinyl]cyclohexanone in a manner similar to Example 15. The crude material was crystallized from diethyl ether to give the Z-isomer in a 24% yield (mp: 178-179 °C).
Calc'd. for $C_{25}H_{32}N_2O_3 \cdot 0.05H_2O$: C, 73.34%; H, 7.91%; N, 6.85.
Found: C, 73.04%; H, 7.91%; N, 7.25.
The E-isomer was isolated from the mother liquors of the above compound by flash chromatography on silica gel eluting with methanol/methylene chloride (1:50) to give the E-isomer in 3.4% yield (m.p 126-128 °C).
Calc'd. for $C_{25}H_{32}N_2O_3 \cdot 0.05\ H_2O$: C,73.34; H,7.91; N,6.85.
Found: C, 72.90; H, 7.91; N, 7.25.

EXAMPLE 21

Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(3-methoxyphenyl)methyl]-1-piperazinyl]cyclohexanol

A mixture of 3-methoxybenzyl chloride (0.24 g, 1.5 mmole), Z-1-(1,3-benzodioxol-5-yl)-4-(1-piperazinyl)-cyclohexanol (0.45 g, 1.5 mmole) and excess potassium carbonate in acetonitrile (20 ml) was heated at reflux for 72 hr. The insolubles were removed, the solution concentrated *in vacuo* and the residue crystallized from isopropyl acetate to give the product (0.38 g, 60.3%, mp: 166-167 °C).
Calc'd. for $C_{25}H_{32}N_2O_4$: C, 70.73%; H, 7.60%; N, 6.60%.
Found: C, 70.58%; H, 7.47%; N, 6.51%.

EXAMPLE 22

Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(3-fluorophenyl)methyl]-1-piperazinyl]cyclohexanol

This compound was prepared from Z-1-(1,3-benzodioxol-5-yl)-4-(1-piperazinyl)cyclohexanol and 3-fluorobenzyl chloride in a manner similar to example 21. The crude product was recrystallized from isopropyl acetate to give a white solid (74.1%, mp: 159-160 °C).
Calc'd. for $C_{24}H_{29}FN_2O_3 \cdot 0.2H_2O$: C, 69.28%; H, 7.13%; N, 6.74%.
Found: C, 68.97%; H, 6.96%; N, 6.58%.

EXAMPLE 23

Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2-fluorophenyl)methyl]-1-piperazinyl]cyclohexanol

This compound was prepared from Z-1-(1,3-benzodioxol-5-yl)-4-(1-piperazinyl)cyclohexanol and 2-fluorobenzyl chloride in a manner similar to example 21. The crude product was recrystallized from

isopropyl acetate to give a white solid (72.5%, mp: 160-161 °C).
Calc'd. for $C_{24}H_{29}FN_2O_3$: C, 69.88%; H, 7.09%; N, 6.62%.
Found: C, 69.79%; H, 7.08%; N, 6.62%

EXAMPLE 24

Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2-methylphenyl)methyl]-1-piperazinyl]cyclohexanol

This compound was prepared from Z-1-(1,3-benzodioxol-5-yl)-4(1-piperazinyl)cyclohexanol and 2-methylbenzyl chloride in a manner similar to example 21. The crude product was recrystallized from isopropyl acetate to give a white solid (82%, mp: 168-170 °C).
Calc'd. for: $C_{25}H_{32}N_2O_3 \cdot 0.2H_2O$: C,72.86%; H, 7.93%; N, 6.80%; H_2O, 0.87%.
Found: C, 73.02%; H, 7.91%; N, 6.67%; H_2O, 0.46%

EXAMPLE 25

Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2-nitrophenyl)methyl]-1-piperazinyl]cyclohexanol

This compound was prepared from Z-1-(1,3-benzodioxol-5-yl)-4-(1-piperazinyl)cyclohexanol and 2-nitrobenzyl chloride in a manner similar to example 21. The crude product was recrystallized from isopropyl acetate to give a white solid (72.7%, mp: 200-201 °C).
Calc'd. For $C_{24}H_{29}N_3O_5$: C, 65.59%; H, 6.66%; N, 9.57%.
Found: C, 65.51%; H, 6.69%; N, 9.45%.

EXAMPLE 26

Z-1-(1,3-Benzodioxol-5-yl)-4-[4-(2-thienylmethyl)-1-piperazinyl]cyclohexanol

A solution of Z-1-(1,3-benzodioxol-5-yl)-4-(1-piperazinyl)cyclohexanol (0.6 g, 2 mmole), thiophene-2-carboxaldehyde (0.22 g, 2 mmole) and sodium cyanoborohydride (0.12 g, 2 mmole) in ethanol (20 ml) was heated at reflux for 36 hr. Water (5 ml) was added to the solution and the ethanol removed *in vacuo*. The residue was extracted with methylene chloride. The extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was recrystallized from isopropyl acetate to give a beige solid (0.39 g, 48.8%, mp: 161-163 °C).
Calc'd. for $C_{22}H_{28}N_2O_3S$: C, 65.97%; H, 7.05%; N, 6.99%.
Found: C, 65.94%; H, 7.05%; N, 6.97%

EXAMPLE 27

Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2-chlorophenyl)methyl]-1-piperazinyl]cyclohexanol

This compound was prepared from Z-1-(1,3-benzodioxol-5-yl)-4-(1-piperazinyl)cyclohexanol and 2-chlorobenzaldehyde in a manner similar to example 26. The crude product was recrystallized from isopropyl acetate to give a white solid (62.5%, mp: 174-175 °C).
Calc'd. for $C_{24}H_{29}ClN_2O_3$: C, 67.21%; H, 6.82%; N, 6.54%.
Found: C, 66.89%; H, 6.86%; N, 6.51%

EXAMPLE 28

Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2,5-dichlorophenyl)methyl]-1-piperazinyl]cyclohexanol

This compound was prepared from Z-1-(1,3-benzodioxol-5-yl)-4-(1-piperazinyl)cyclohexanol and 2,5-dichlorobenzyl chloride in a manner similar to example 21. The crude product was recrystallized from isopropyl ether to give a white solid (65.2%, mp: 158-159 °C).
Calc'd. For $C_{24}H_{28}Cl_2N_2O_3$: C, 62.20%; H, 6.09%; N, 6.05%.
Found: 62.26%; H, 6.11%; N, 5.96%.

EXAMPLE 29

Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2,5-difluorophenyl)methyl]-1-piperazinyl]cyclohexanol

This compound was prepared from Z-1-(1,3-benzodioxol-5-yl)-4-(1-piperazinyl)cyclohexanol and 2,5-difluorobenzyl bromide in a manner similar to example 21. The crude product was recrystallized from isopropyl acetate to give a white solid (46.0%, mp: 154-156 °C).
Calc'd. For $C_{24}H_{28}F_2N_2O_3 \cdot 0.2H_2O$: C, 66.40%; H, 6.60%; N, 6.45%.
Found: 66.39%; H, 6.50%; N, 6.46%.

EXAMPLE 30

Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2,3-difluorophenyl)methyl]-1-piperazinyl]cyclohexanol

This compound was prepared from Z-1-(1,3-benzodioxol-5-yl)-4-(1-piperazinyl)cyclohexanol and 2,3-difluorobenzyl bromide in a manner similar to example 21. The crude product was recrystallized from isopropyl acetate to give a white solid (88.5%, mp: 159-160 °C).
Calc'd. For $C_{24}H_{28}F_2N_2O_3 \cdot 0.1H_2O$: C, 66.68%; H, 6.58%; N, 6.48%.
Found: 66.46%; H, 6.51%; N, 6.28%.

EXAMPLE 31

Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(3,5-difluorophenyl)methyl]-1-piperazinyl]cyclohexanol

This compound was prepared from Z-1-(1,3-benzodioxol-5-yl)-4-(1-piperazinyl)cyclohexanol and 3,5-difluorobenzyl bromide in a manner similar to example 21. The crude product was recrystallized from isopropyl acetate to give a white solid (38.6%, mp: 160-161 °C).
Calc'd. For $C_{24}H_{28}F_2N_2O_3 \cdot 0.1H_2O$: C, 66.68%; H, 6.58%; N, 6.48%.
Found: 66.46%; H, 6.51%; N, 6.23%.

EXAMPLE 32

Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2-iodophenyl)methyl]-1-piperazinyl]cyclohexanol

This compound was prepared from Z-1-(1,3-benzodioxol-5-yl)-4-(1-piperazinyl)cyclohexanol and 2-iodobenzyl bromide in a manner similar to example 21. The crude product was recrystallized from isopropyl acetate to give a white solid (67.3%, mp: 168-171 °C).
Calc'd. For $C_{24}H_{29}IN_2O_3$: C, 55.40%; H, 5.62%; N, 5.38%.
Found: 55.76%; H, 5.55%; N, 5.37%.

EXAMPLE 33

Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(1,3-benzodioxo-4-yl)methyl]-1-piperazinyl]cyclohexanol

This compound was prepared from Z-1-(1,3-benzodioxol-5-yl)-4-(1 piperazinyl)cyclohexanol and 2,3-methyenedioxybenzyl chloride in a manner similar to example 21. The crude product was recrystallized from isopropyl acetate to give a white solid (83.3%, mp: 163-164 °C).
Calc'd. For $C_{25}H_{30}N_2O_5$: C, 68.47%; H, 6.90%; N, 6.39%.
Found: 68.20%; H, 6.85%; N, 6.29%.

EXAMPLE 34

Z-1-(4-Fluorophenyl)-4-[4-[(3-methoxyphenyl)methyl]-1-piperazinyl]cyclohexanol

This compound was prepared from Z-1-(4-fluorophenyl)-4-(1-piperazinyl)cyclohexanol and 3-methoxybenzyl chloride in a manner similar to example 21. The crude product was recrystallized from isopropyl acetate to give a white solid (62.5%, mp: 162-163 °C).
Calc'd. For $C_{24}H_{31}FN_2O_2 \cdot 0.2H_2O$: C, 71.68%; H, 7.87%; N, 6.97%.

Found: 71.57%; H, 7.82%; N, 6.91%.

EXAMPLE 35

Z-1-(4-Fluorophenyl)-4-[4-[(2-chlorophenyl)methyl]-1-piperazinyl]cyclohexanol

This compound was prepared from Z-1-(4-fluorophenyl)-4-(1-piperazinyl)cyclohexanol and 2-chlorobenzyl chloride in a manner similar to example 21. The crude product was recrystallized from isopropyl acetate to give a white solid (80.2%, mp: 164-165 °C).
Calc'd. For $C_{23}H_{28}ClFN_2O$: C, 68.56%; H, 7.00%; N, 6.95%.
Found: 68.28%; H, 6.92%; N, 6.86%.

EXAMPLE 36

Z-1-(4-Fluorophenyl)-4-[4-[(2,5-difluorophenyl)methyl]-1-piperazinyl]cyclohexanol

This compound was prepared from Z-1-(4-fluorophenyl)-4-(1-piperazinyl)cyclohexanol and 2,5-difluorobenzyl bromide in a manner similar to example 21. The crude product was recrystallized from isopropyl acetate to give a white solid (84.3%, mp: 149-151 °C).
Calc'd. For $C_{23}H_{27}F_3N_2O \cdot 0.5H_2O$: C, 66.81%; H, 6.83%; N, 6.78%.
Found: 66.46%; H, 6.50%; N, 6.64%.

EXAMPLE 37

Z-1-[(4-Trifluoromethyl)phenyl]-4-[4-[(2-chlorophenyl)methyl]-1-piperazinyl]cyclohexanol

This compound was prepared from Z-1-[(4-trifluoro-methyl)phenyl]-4-(1-piperazinyl)cyclohexanol and 2-chlorobenzyl chloride in a manner similar to example 21. The crude product was recrystallized from isopropyl ether to give a beige solid (45.2%, mp: 161-162 °C).
Calc'd. For $C_{24}H_{28}ClF_3N_2O$: C, 63.64%; H, 6.23%; N, 6.19%.
Found: 63.26%; H, 6.27%; N, 6.20%.

EXAMPLE 38

Z-1-[(4-Trifluoromethyl)phenyl]-4-[4-[(3-methoxyphenyl)methyl]-1-piperazinyl]cyclohexanol

This compound was prepared from 4-[4-(trifluoromethyl)phenyl]-4-hydroxycyclohexanone, titanium isopropoxide, sodium borohydride and (3-methoxybenzyl)piperazine in a manner similar to example 5. The crude product was recrystallized from isopropyl ether to give a beige solid (46.4%, mp: 131-132 °C).
Calc'd. For $C_{25}H_{31}F_3N_2O_3 \cdot 0.45H_2O$: C, 65.75%; H, 7.04%; N, 6.13%.
Found: 65.45%; H, 6.58%; N, 6.66%.

EXAMPLE 39

Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2-fluoro-5-methoxyphenyl) methyl]-1-piperazinyl]cyclohexanol

This compound was prepared from 4-(1,3-benzodioxol-5-yl)-4-hydroxycyclohexanone, titanium isopropoxide, sodium borohydride and (2-fluoro-5-methoxybenzyl)piperazine in a manner similar to example 5. The crude product was recrystallized from isopropyl ether to give a white solid (16.4%, mp: 136-137 °C).
Calc'd. For $C_{25}H_{31}FN_2O_4$: C, 67.85%; H, 7.06%; N, 6.33%.
Found: 67.41%; H, 6.91%; N, 6.36%.

EXAMPLE 40

Z-1-(4-Fluorophenyl)-4-[4-[(2-fluoro-5-methoxyphenyl)methyl]-1-piperazinyl]cyclohexanol

This compound was prepared from 4-(4-fluorophenyl)-4-hydroxycyclohexanone, titanium isopropoxide, sodium borohydride and (2-fluoro-5-methoxybenzyl)piperazine in a manner similar to example 5. The crude

product was recrystallized from isopropyl acetate to give a white solid (21.1%, mp: 159-161 °C).
Calc'd. For $C_{24}H_{30}F_2N_2O_2$: C, 69.21%; H, 7.26%; N, 6.73%.
Found: 69.52%; H, 7.41%; N, 6.81%.

EXAMPLE 41

Z-1-(1,4-Benzodioxan-6-yl)-4-[4-[(3-methoxyphenyl)methyl]-1-piperidinyl]cyclohexanol

This compound was prepared from 4-(1,4-benzodioxan-6-yl)-4-hydroxycyclohexanone, titanium isopropoxide, sodium borohydride and 4-(3-methoxybenzyl)piperidine in a manner similar to example 5. The crude product was recrystallized from isopropyl acetate to give a white solid (5.0%, mp: 183-185 °C).
Calc'd. For $C_{27}H_{35}NO_4 \cdot 0.5H_2O$: C, 72.61%; H, 8.13%; N, 3.14%.
Found: 72.33%; H, 7.94%; N, 3.02%.

EXAMPLE 42

Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(3-methoxyphenyl)methyl]-1-piperidinyl]cyclohexanol

This compound was prepared from 4-(1,3-benzodioxol-5-yl)-4-hydroxycyclohexanone, titanium isopropoxide, sodium borohydride and 4-(3-methoxybenzyl)piperidine in a manner similar to example 5. The crude product was recrystallized from isopropyl acetate to give a white solid (4.9%, mp: 164-165 °C).
Calc'd. For $C_{26}H_{33}NO_4$: C, 73.73%; H, 7.85%; N, 3.31%.
Found: 73.45%; H, 7.88%; N, 3.20%.

EXAMPLE 43

Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2,5-difluorophenyl)methyl]-1-piperidinyl]cyclohexanol

This compound was prepared from 4-(1,3-benzodioxol-5-yl)-4-hydroxycyclohexanone, titanium isopropoxide, sodium borohydride and 4-(2,5-difluorobenzyl)piperidine in a manner similar to example 5. The crude product was recrystallized from isopropyl ether to give a white solid (38.5%, mp: 167-168 °C).
Calc'd. For $C_{25}H_{29}F_2NO_3$: C, 69.91%; H, 6.81%; N, 3.26%.
Found: 69.82%; H, 6.71%; N, 3.24%.

EXAMPLE 44

Z-1-[4-(1,3-Benzodioxol-5-yl)-4-methoxy-1-cyclohexyl]-4-[(3-methoxyphenyl)methyl]piperidine

This compound was prepared from 4-(1,3-benzodioxol-5-yl)-4-methoxycyclohexanone, titanium isopropoxide, sodium borohydride and 4-(3-methoxybenzyl)piperidine in a manner similar to example 5. The crude product was recrystallized from hexane to give a white solid (78%, mp: 89-90 °C).
Calc'd. For $C_{27}H_{35}NO_4$: C, 74.11%; H, 8.06%; N, 3.20%.
Found: 73.89%; H, 8.00%; N, 3.15%.

EXAMPLE 45

Z-1-[4-(1,4-Benzodioxan-6-yl)-4-methoxy-1-cyclohexyl]-4-[3-(methoxyphenyl)methyl]piperidine fumarate

This compound was prepared from 4-(1,4-benzodioxan-6-yl)-4-methoxycyclohexanone, titanium isopropoxide, sodium borohydride and 4-(3-methoxybenzyl)piperidine in a manner similar to example 5. The crude product was converted to the fumarate salt in ethyl acetate-methanol to give a white solid (16.7%, mp: 165-170 °C).
Calc'd. For $C_{28}H_{37}NO_4 \cdot C_4H_4O_4$: C, 67.70%; H, 7.28%; N, 2.47%.
Found: 67.29%; H, 7.10%; N, 2.46%.

EXAMPLE 46

Z-1-[4-(1,3-Benzodioxol-5-yl)-4-methoxy-1-cyclohexyl]-4-[(2,5-difluorophenyl)methyl]piperidine fumarate

This compound was prepared from 4-(1,3-benzodioxol-5-yl)-4-methoxycyclohexanone, titanium isopropoxide, sodium borohydride and 4-(2,5-difluorobenzyl)piperidine in a manner similar to example 5. The crude material was converted to the fumarate salt in acetone to give a white solid (38.5%, mp: 189-190 °C).
Calc'd. For $C_{26}H_{31}F_2NO_3 \cdot C_4H_4O_4 \cdot 0.1H_2O$: C, 64.18%; H, 6.32%; N, 2.50%.
Found: C, 63.93%; H, 6.27%; N, 2.53%.

EXAMPLE 47

Z-1-(4-Fluorophenyl)-4-[4-(phenylmethyl)-1-piperidinyl]cyclohexanol

This compound was prepared from 4-(4-fluorophenyl)-4-hydroxycyclohexanone, titanium isopropoxide, sodium borohydride and 4-benzylpiperidine in a manner similar to example 5. The crude product was recrystallized from isopropyl acetate to give a white solid (44.4%, mp: 160-161 °C).
Calc'd. For $C_{24}H_{30}FNO \cdot 0.2H_2O$: C, 77.67%; H, 8.26%; N, 3.78%.
Found: 77.74%; H, 8.13%; N, 3.78%.

EXAMPLE 48

Z-1-(4-Fluorophenyl)-4-[4-[(3-methoxyphenyl)methyl]-1-piperidinyl]cyclohexanol

This compound was prepared from 4-(4-fluorophenyl)-4-hydroxycyclohexanone, titanium isopropoxide, sodium borohydride and 4-(3-methoxybenzyl)piperidine in a manner similar to example 5. The crude product was recrystallized from isopropyl acetate to give a white solid (12.5%, mp: 169-170 °C).
Calc'd. For $C_{24}H_{32}FNO_2 \cdot 0.5H_2O$: C, 73.86%; H, 8.18%; N, 3.45%.
Found: 73.93%; H, 7.93%; N, 3.44%.

EXAMPLE 49

Z-1-(4-Fluorophenyl)-4-[4-[(2,5-difluorophenyl)methyl]-1-piperidinyl]cyclohexanol

This compound was prepared from 4-(4-fluorophenyl)-4-hydroxycyclohexanone, titanium isopropoxide, sodium borohydride and 4-(2,5-difluorobenzyl)piperidine in a manner similar to example 5. The crude product was recrystallized from isopropyl ether to give a white solid (61.5%, mp: 162-163 °C).
Calc'd. For $C_{24}H_{28}F_3NO$: C, 71.44%; H, 7.00%; N, 3.47%.
Found: 71.23%; H, 7.12%; N, 3.42%.

EXAMPLE 50

Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2-bromophenyl)methyl] 1-piperazinyl]cyclohexanol

This compound was prepared from Z-1-(1,3-benzodioxol-5-yl)-4-(1-piperazinyl)cyclohexanol and 2-bromobenzyl bromide in a manner similar to example 21. The crude product was recrystallized from isopropyl acetate to give a white solid (84.5%, mp: 169-170 °C).
Calc'd. For $C_{24}H_{29}BrN_2O_3$: C, 60.90%; H, 6.18%; N, 5.92%.
Found: 61.26%; H, 6.25%; N, 5.82%.

EXAMPLE 51

Z-1-(1,3-Benzodioxol-5-yl)-4-[4-(diphenylmethyl)-1-piperazinyl]cyclohexanol

This compound was prepared from Z-1-(1,3-benzodioxol-5-yl)-4-(1-piperazinyl)cyclohexanol and chlorodiphenylmethane in a manner similar to example 21. The crude product was recrystallized from isopropyl acetate to give a white crystals (87.8%, mp: 210-211 °C).

Calc'd. For $C_{30}H_{34}N_2O_3 \cdot 0.3H_2O$: C, 75.70%; H, 7.33%; N, 5.89%.
Found: 75.48%; H, 7.26%; N, 5.96%.

EXAMPLE 52

Z-1-(1,3-Benzodioxol-5-yl)-4-[4-(1-phenylethyl)-1-piperazinyl]cyclohexanol

This compound was prepared from Z-1-(1,3-benzodioxol-5-yl)-4-(1-piperazinyl)cyclohexanol, titanium isopropoxide, sodium borohydride and acetophenone in a manner similar to example 5. The crude product was recrystallized from isopropyl acetate to give a white solid (90%, mp: 177-178 °C).
Calc'd. For $C_{25}H_{32}N_2O_3 \cdot 0.3H_2O$: C, 72.86%; H, 7.93%; N, 6.80%.
Found: 72.74%; H, 7.76%; N, 6.76%.

EXAMPLE 53

Z-1-[4-(4-Fluorophenyl)-4-methoxy-1-cyclohexyl]-4-[(3-methoxyphenyl)methyl]piperazine

Step 1

Sodium hydride (1.27 g, 31.7 mmole) was added to a solution of 8-(4-fluorophenyl)-1,4-dioxaspiro[4.5]-decan-8-ol (8.0 g, 10 mmole) in THF (100 ml) and the mixture stirred for 16 hr and heated at reflux for 4 hr. The solution was cooled to 25 °C and iodomethane (6.75 g, 47.6 mmole) was added. The mixture was stirred for 112 hr and concentrated *in vacuo*. The residue was suspended in water and the mixture extracted with methylene chloride. The extracts were dried and concentrated *in vacuo* to give 8-(4-fluorophenyl)-1,4-dioxaspiro[4.5]decan-8-ol methyl ether (98.8%, mp: 52-54 °C).

Step 2

A solution of 8-(4-fluorophenyl)-1,4-dioxaspiro[4.5]decan-8-ol methyl ether in acetone (200 ml) was stirred for 96 hr with p-toluenesulfonic acid (0.1 g) and the solution diluted with saturated $NaHCO_3$ solution. The mixture was concentrated *in vacuo* and the residue suspended in water. The mixture was extracted with ether and the ether extracts dried and concentrated *in vacuo*. The residue was crystallized from hexane to give 4-(4-fluoro-phenyl)-4-methoxycyclohexanone (94%, mp: 57-59 °C).

Step 3

A mixture of 4-(4-fluorophenyl)-4-methoxycyclohexanone (2,2 g, 10 mmole), phenylmethyl 1-piperazinecarboxylate (2.2 g, 10 mmole), titanium(IV) isopropoxide (3.7 ml, 11 mmole) were mixed, reacted and reduced with sodium borohydride (0.4 g, 10 mmole) as in example 5. The crude product was purified by chromatography on silica eluting with methanol-methylene chloride (1:50) to give phenylmethyl [4-(4-fluorophenyl)-4-methoxy-1-cyclohexyl]-1-piperazinecarboxylate (35.7%, mp: 68-69 °C).

Step 4

A mixture of phenylmethyl [4-(4-fluorophenyl)-1-methoxy-1-cyclohexyl]-1-piperazinecarboxylate (1.25 g, 2.9 mmole) and 10% palladium on charcoal (0.2 g) in methanol (50 ml) was hydrogenated for 2 hr. The catalyst was removed and the solution concentrated *in vacuo*. The material was crystallized from hexane to give 1-[4-(4-fluorophenyl)-4-methoxy-1-cyclohexyl]piperazine (73.8%).

Step 5

A mixture of 1-[4-(4-fluorophenyl)-4-methoxy-1-cyclohexyl]-piperazine(0.33 g, 1.1 mmole) and 3-methoxybenzyl bromide (0.18 g, 1.1 mmole) was reacted as in example 13. The crude material was crystallized from hexane to give the product (37.8%, mp: 92-93 °C).
Calc'd. For $C_{24}H_{33}FN_2O_2$: C, 72.79%; H, 8.07%; N, 6.80%.
Found: 72.73%; H, 8.15%; N, 6.71%.

EXAMPLE 54

Z-1-[4-(4-Fluorophenyl)-4-methoxy-1-cyclohexyl]-4-[(2-chlorophenyl)methyl]piperazine

A mixture of 1-(4-fluorophenyl)-1-methoxypiperazine (0.33 g, 1.1 mmole) and 2-chlorobenzyl chloride (0.18 g, 1.1 mmole) was reacted as in example 13. The crude material was crystallized from hexane to give the product (44.4%, mp: 66-67 °C).
Calc'd. For $C_{24}H_{30}FN_2O$: C, 68.25%; H, 7.31%; N, 6.64%.
Found: 68.07%; H, 7.18%; N, 6.50%.
Table 1 shows the *in vitro* receptor binding affinities of the compounds made in Examples 15 through 52.

TABLE 1
IN VITRO RECEPTOR BINDING ACTIVITIES

EXAMPLE	5-HT_{1A} (nM)	D_2 (nM)
15	5.4	>1000
16	15.6	2,710
17	20	1,710
18	46.5	1,830
19	14	1,350
20-Z	9.9	15,200
20-E	5.3	---
21	2.15	1,040
22	13.4	---
23	10.1	1,540
24	4.2	2,550
25	12.8	7,080
26	19.1	---
27	1.85	---
28	0.6	---
29	2.6	---
30	17.3	---
31	21.1	---
32	1.2	---
33	34.9	---
34	10.6	---
35	5.9	---
36	34.7	---
37	25.8	---
38	35.6	---
39	0.75	---
40	3.45	---
41	2.2	---
42	4.4	---
43	4.9	---
44	8.2	---
45	3.4	---
46	16.2	---
47	59.8	---
48	31.9	---
49	57.6	---
50	1.2	---
51	28.6	---
52	18.1	---

Table 2 shows the *in vivo* activity of the compounds made in Examples 7 through 50 in the rat social interaction task.

TABLE 2

IN VIVO ACTIVITY	
EXAMPLE	RAT SOCIAL INTERACTION TASK
	Active doses
15	0.01-.1 mpk
17	0.1-1.0 mpk
18	0.1-1.0 mpk
19	0.1 mpk
20-Z	0.001-0.01 mpk
36	0.01-10 mpk
44	0.001-0.01 mpk
49	0.1 mpk
50	0.01-0.1 mpk

The compounds comprising the present invention are selective antagonists and partial agonists at the serotonergic 5-HT_{1A} receptor. Serotonergic pathways are implicated in a variety of psychiatric disorders such as anxiety and panic disorders, and it is known that antagonists of the 5-HT_{1A} receptor are clinically effective in the treatment of anxiety (see: D.P. Taylor, "Serotonin Agents in Anxiety," *Annals of the New York Academy of Sciences* vol. 600, entitled: "The Neuropharmacology of Serotonin," pp 545-557, October 15, 1990.) Furthermore, there is evidence that 5-HT_{1A} agents may be useful in the prophylactic treatment of migraine (see: J. Pascual and J. Berciano, "An Open Trial of Buspirone in Migraine Prophylaxis. Preliminary Report," *Clinical Neuropharmacology* 14:3, 1991, pp. 245-250.) Compounds of the present invention are thus envisioned to be useful in the treatment of disorders such as anxiety, panic disorders, obsessive-compulsive disorder, and depression, as well as in the prophylactic treatment of migraine.

In vitro IC_{50} test values for binding to the 5-HT_{1A} receptor were determined for representative compounds of Formula I by the method of S.J. Peroutka, Brain Research 344, 167 (1985); with only minor modifications. Test IC_{50} values lower than 100 nM are considered to reflect activity at the 5-HT_{1A} receptor. Compounds with IC_{50} values lower than 20 nM comprise the preferred compounds.

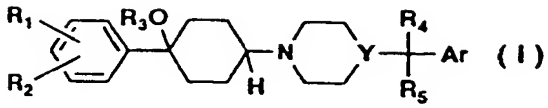
The social interaction task is an *in vivo* model of anxiety (see: A.P. Guy and C.R. Gardner, "Pharmacological characterization of a modified social interaction model of anxiety in the rat," Neuropsychobiology 13: 194-200, 1985.) Compounds of the present invention are active in this *in vivo* model of anxiety when given subcutaneously in doses of 0.1-1.0 mg/kg, thus providing additional evidence that the present compounds will be useful in the treatment of anxiety and panic disorders.

It is also known that agents which interact with dopaminergic receptors can produce movement disorders and other extrapyramidal side effects (see: R.J. Baldessarini," Drugs and the Treatment of Psychiatric Disorders," in "*Goodman and Gilman's: The Pharmacologic Basis of Therapeutics*," 8th ed., p. 428, A.G. Goodman, T.W. Rall, A.S. Nies, and P. Taylor, Editors, Pergamon Press, Inc., Fairview Park, N.Y., 1990). The compounds of the present invention are inactive at the dopaminergic receptors at the doses used to treat disorders such as anxiety, thus the risk of extrapyramidal side effects is small.

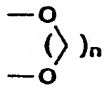
In vitro IC_{50} test values for binding to the D_2 receptor were determined for representative compounds of Formula I by the method of Burt, Creese, and Snyder, Molecular Pharmacology 12, 800 (1976); Creese, Burt, and Snyder, Science 196, 326 (1977); and Creese, Burt and Snyder, Science 192, 481 (1976). Test IC_{50} values greater than 1,000 nM are considered to reflect inactivity at the D_2 receptor, indicating the risk of extrapyramidal side effects is small. Compounds with IC_{50} values greater than 1,000 nM comprise the preferred compounds. Reasonable variations, such as those which would occur to a skilled artison, may be made herein without departing from the scope of the invention.

Claims

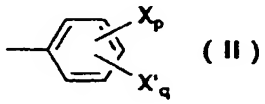
1. A compound of Formula I or a pharmaceutically acceptable salt thereof, with Formula I being:



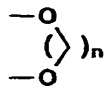
wherein R_1 and R_2 are independently selected from H, halogen, CF_3, or C_{1-4} alkoxy groups except that R_1 and R_2 cannot both be H simultaneously, and R_1 and R_2, when on adjacent carbon atoms, can be taken together to form a



bridge with n being an integer from 1 to 3;
R_3 is H or C_{1-4} alkyl;
R_4 and R_5 are each independently selected from H, C_{1-4} alkyl or phenyl;
Y is N or CH; and
Ar is a heteroaryl, an unsubstituted phenyl ring, or a substituted phenyl ring of structure II:

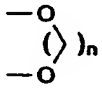


wherein X and X' may be halogen, nitro, amino, carboxamide, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} alkylthio or X and X' can be taken together to form a



bridge (n = 1-3).

2. The compound of claim 1 wherein R_1 and R_2 taken together form the bridge



(n = 1-3).

3. The compound of claim 2 wherein each of R_3, R_4 and R_5 is H.

4. The compound of claim 3 wherein Y is CH.

5. The compounds of claim 4 selected from the group consisting of:
Z-1-(1,3-Benzodioxol-5-yl)-4-[4-(phenylmethyl)-1-piperidinyl]cyclohexanol;
Z-1-(4-Methoxyphenyl)-4-[4-(phenylmethyl)-1-piperidinyl]cyclohexanol;
Z-1-(4-Fluorophenyl)-4-[2,5-difluorophenyl)methyl)-1-piperidinyl)cyclohexanol;
Z-1-[4-(1,3-Benzodioxol-5-yl)-4-methoxy-1-cyclohexyl]4-[3-methoxyphenyl)methyl)piperidine;
Z-1-(4-Fluorophenyl)-4-[4-(phenylmethyl)-1-piperidinyl]cyclohexanol;
Z-1-(4-Fluorophenyl)-4-[4-(3-methoxyphenyl)methyl]-1-piperidinyl]cyclohexanol;

Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2,5-difluorophenyl)methyl]-1-piperidinyl)cyclohexanol;
Z-1-(1,4-Benzodioxan-6-yl)-4-[4-[(3-methoxyphenyl)methyl]-1-piperidinyl)cyclohexanol;
Z-1-[4-(1,4-Benzodioxan-6-yl)-4-methoxy-1-cyclohexyl]-4-[3-(methoxyphenyl)methyl)piperidine fumarate;
Z-1-[4-(1,3-Benzodioxol-5-yl)-4-methoxy-1-cyclohexyl]-4-[(2,5-difluorophenyl)methyl]piperidine fumarate;

6. The compounds of claim 3 wherein Y is N.

7. The compound of claim 6 selected from the group consisting of:
Z-1-(4-fluorophenyl)-4-[4-(2,5-difluorophenyl)methyl)-1-piperazinyl]cyclohexanol;
Z-1-(1,3-benzodioxol-5-yl)-4-[4-[(2-fluoro-5-methoxyphenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(4-fluorophenyl)-4-[4-[(2-fluoro-5-methoxyphenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1(1,3-benzodioxol-5-yl)-4-[4-(phenylmethyl)-1-piperazinyl)cyclohexanol;
Z-1-(4-methoxyphenyl)-4-[4-(phenylmethyl)-1-piperazinyl]cyclohexanol;
Z-1-[4-(1,3-benzodioxol-5-yl)-4-methoxycyclohexyl]-4-(phenylmethyl)piperazine;
Z-1-(1,4-benzodioxan-6-yl)-4-[4-(phenylmethyl)-1-piperazinyl]cyclohexanol;
Z-1-(1,3-benzodioxol-5-yl)-4-[4-[(3-methoxyphenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-benzodioxol-5-yl)-4-[4-[(3-fluorophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-benzodioxol-5-yl)-4-[4-[(2-fluorophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1 (1,3-benzodioxol-5-yl)-4-[4-[(2-methylphenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-benzodioxol-5-yl)-4-[4-[(2-nitrophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-benzdioxol-5-yl)-4-[4-[(2-chlorophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2,5-dichlorophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2,5-difluorophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2-bromophenyl)methyl]-1-piperazinyl]cyclohexanol.
Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2,3-difluorophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(3,5-difluorophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(2-iodophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-Benzodioxol-5-yl)-4-[4-[(1,3-benzodioxo-4-yl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(1,3-Benzodioxol-5-yl)-4-[4-(diphenylmethyl)-1-piperazinyl]cyclohexanol;
Z-1-(1,3-Benzodioxol-5-yl)-4-[4-(1-phenylethyl)-1-piperazinyl]cylohexanol;
Z-1-(4-Fluorophenyl)-4-[4-[(3-methoxyphenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-(4-Fluorophenyl)-4-[4-[(2-chlorophenyl)methyl]-1-piperazinyl]cyclohexanol;
Z-1-[4-(4-Fluorophenyl)-4-methoxy-1-cyclohexyl]-4-[(-3-methoxyphenyl)methyl]piperazine,
Z-1-(1,3-benzodioxol-5-yl)-4-[4-(2-thienylmethyl)-1-piperazinyl]cyclohexanol.

8. A pharmaceutical composition comprising at least one compound of any one of claims 1 to 7 and a pharmaceutically acceptable carrier.

9. The use of at least one compound of any one of claims 1 to 7 for preparing a pharmaceutical composition for treating anxiety.

10. The use of at least one compound of any one of claims 1 to 7 for preparing a pharmaceutical composition for the prophylactic treatment of migraines.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 12 1199

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,Y	EP-A-0 431 580 (WARNER-LAMBERT COMPANY) 12 June 1991 *see whole document* ---	1-10	C07D211/14 C07D211/22 C07D211/18 C07D319/18
D,Y	EP-A-0 431 579 (WARNER-LAMBERT COMPANY) 12 June 1991 *see whole document* ---	1-10	C07D317/54 C07D405/08 C07D409/12 C07D295/084
Y	EP-A-0 035 902 (JANSSEN PHARMACEUTICA N.V.) 16 September 1981 *see whole document, especially pages 16-20* ---	1-10	A61K31/44 A61K31/495
Y	JOURNAL OF MEDICINAL CHEMISTRY vol. 16, no. 11, 1973, pages 1251 - 1256; 'PARTLY REDUCED BIPHENYLS AS CENTRAL NERVOUS SYSTEM AGENTS.' *see especially compounds of formula 15, page 1252, and column 1, page 1252* ---	1-10	
Y	US-A-3 965 180 (THE UPJOHN COMPANY) 22 June 1976 ---	1-10	
A	US-A-5 036 070 (AMERICAN HOME PRODUCTS CORPORATION) 30 July 1991 ---	1-10	TECHNICAL FIELDS SEARCHED (Int. Cl.5) C07D
A	WO-A-9 113 872 (THE UPJOHN COMPANY) 19 September 1991 ---	1-10	A61K
A	EP-A-0 208 235 (MERRELL DOW PHARMACEUTICALS INC.) 14 January 1987 -----	1-10	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	18 FEBRUARY 1993	SCRUTON-EVANS I.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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